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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/187,385	11/06/1998	SVETOMIR N. MARKOVIC	07039/119001	2986

26191 7590 11/03/2004

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/187,385	MARKOVIC, SVETOMIR N.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,12,18,21,22,26,27,30-32,35-38 and 41-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,12,18,21,22,26,27,30-32,35,38 and 41-56* is/are rejected.

7)☒ Claim(s) *36 and 37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 2, 2004 has been entered.

2. Claims 8, 12, 18, 21, 22, 26, 27, 30-32, 35-38 and 41-56 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The rejection of claims 26, 8-12, 18, 21, and 22 under 35 U.S.C. 103(a) as being unpatentable over Tovey et al (U.S. Patent 5,997,858; issued Dec. 7, 1999; filed May 9, 1997) in view of Brittenden et al (Brittenden, J. et al. Cancer, 77(7): 1226-1243, 1996, April) is withdrawn in view of the amendment to the claims.

5. The rejection of claims 27 and 30-38 under 35 U.S.C. 103(a) as being unpatentable over Markovic et al[a] (Markovic, S.N. et al, Int. J. Cancer, 45: 788-794, 1990; IDS ref. "CH") in

view of Tovey et al (U.S. Patent 5,997,858; issued Dec. 7, 1999; filed May 9, 1997) is withdrawn for the reasons of record.

New Grounds of Rejection:

5. Claims 41-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that new claims 41-56 are not supported in the specification as originally filed and, thus, introduce new matter into the specification.

Independent claim 41 is drawn to method for stimulating the immune system of a human patient, comprising administering α-interferon at a dosage of between 250,000 U/m^2 to about 500, 000U/m^2; determining whether the natual killer lymphocyte cytoxoticity of said patient is increased at least about 75% above baseline level of natural killer lymphosycte cytoxicity in said patient; and administering to said patient an adjusted immunostimulatory dosage of said α-interferon if said natural kill lymphocyte cytoxicity is not at least about 75% above said baseline natural killer lymphocyte cytotoxicity.

No support for the claimed methods is found in the specification, because the specification teaches that, in a method of identifying an optimal individualized α-interferon immunostimulatory dosage, the cutoff is that the patient's NK lymphocyte toxicity levels are at least 50% higher than the patient's baseline NK lymphocyte toxicity levels at an effector to target (E:T) cell ratio of 25:1. There is no support for methods where the range of patient's NK

lymphocyte toxicity levels is at least 75% higher as recited in the claims. Furthermore, the specification teaches a specific E:T ratio of 25:1 which is missing from the claims. Therefore, the methods of claims 41-56 do not find support in the specification as originally filed.

6. Claims 26, 8, 12, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards (Edwards, B.S. et al, J. Clin. Invest., 75: 1908-1913, 1985; cited in the IDS) in view of Hellstrand (U.S. Patent 6,063,373; issued May 16, 2000; effective filing date of Aug. 8, 1994).

Claims 26, 8, 12 and 22 are drawn to methods for stimulating the immune system of a human patient having a non-resectable malignant tumor comprising determining the natural killer lymphocyte cytotoxicity of said patient to provide a baseline natural killer lymphocyted cytotoxicity; administering an immunostimulatory dosage of an α-interferon composition to said patient, wherein said immunostimulatory dosage increases NK lymphocyte cytotoxicity at least about 75% above said baseline natural killer lymphocyte cytotoxicity; and treating said patient with effective non-surgical medical methodologies to diminish said tumor. The dosage may be administered once per day; the NK lymphocyte cytotoxicity may be measure at an effector to target cell ratio from about 15:1 to about 50:1. The tumor may be selected from the group consisting of breast cancer, lung cancer, pancreatic cancer, brain cancer, prostate cancer, ovarian cancer, uterine cancer, renal cancer, and melanoma.

Edwards teaches a method for determining the optimal α-interferon dosage for the purpose of increasing NK lymphocyte cytotoxicity. Edwards finds that a peak NK cell activation, corresponding to a mean threefold increase above preinjection levels of NK cell

activity results from injection of 3 X 10^6 U injected intramuscularly. Therefore, Edwards teaches a method of establishing a baseline NK lymphocyte cytotoxicity level and then injection of an immunostimulatory dosage of α-interferon increases NK lymphocyte cytotoxicity at least about 75% above said baseline natural killer lymphocyte cytotoxicity. Edwards teaches the method in breast, ovarian, head and neck carcinoma and renal cancer patients. Edwards teaches effector to target cell ratios of 3.125:1, 6,25:1, 12.5:1, 501 and 100:1 (page 1908, 2nd column to 1909, 2nd column). Edwards fails to teach a method that includes a step of then treating the patient with an effective non-surgical methodology to treat a tumor.

However, Hellstrand teaches methods using α-interferon in methods of treatment using other anticancer therapies (column 7, line 5). Further Hellstrand teaches methods where the use of α-interferon is for the purpose of increasing NK cell cytoxicity for the treatment of cancer.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to used the method of Edwards to determine the optimal immunostimulatory dosage of α-interferon and then to use the method of Hellstrand to administer α-interferon in combination with other anticancer treatments. One would have been motivated to combine the teachings of Edwards with Hellstrand because both teach that the NK cell activation of α-interferon is important for the treatment of cancer.

6. Claims 26, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards (Edwards, B.S. et al, J. Clin. Invest., 75: 1908-1913, 1985; cited in the IDS) in view of Hellstrand (U.S. Patent 6,063,373; issued May 16, 2000; effective filing date of Aug. 8, 1994) and further in view of Brittenden (Brittenden, J. et al, Cancer , 77: 1226-1243, 1996; of record).

Claims 26 and 21 read on methods of treating melanoma.

The combination of Edwards and Hellstrand fail to teach or suggest the methods for the treatment of melanoma. However, Brittenden teaches that α-interferon in combination with rIL-2 and cisplatin has been used to treat disseminated melanoma. Brittenden also teaches that α-interferon enhances NK cell activity (page 1234, 2nd column). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Edwards and Hellstrand for the purpose of treating melanoma.

7. Claims 27, 31, 32, 35, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards (Edwards, B.S. et al, J. Clin. Invest., 75: 1908-1913, 1985; cited in the IDS) in view of Nichols (Nichols, P.H. et al. Clin. Exp. Immunol. 94: 4-10, 1993).

Claims 27, 31, 32, 35, and 38 are drawn to methods for stimulating the immune system of a human patient having a resectable malignant tumor comprising determining the natural killer lymphocyte cytotoxicity of said patient to provide a baseline natural killer lymphocyted cytotoxicity; administering an immunostimulatory dosage of an α-interferon composition to said patient, wherein said immunostimulatory dosage increases NK lymphocyte cytotoxicity at least about 75% above said baseline natural killer lymphocyte cytotoxicity; and surgically resecting said malignant tumor. The dosage may be administered once per day; the NK lymphocyte cytotoxicity may be measure at an effector to target cell ratio from about 15:1 to about 50:1. The tumor may be selected from the group consisting of breast cancer, lung cancer, pancreatic cancer, brain cancer, prostate cancer, ovarian cancer, uterine cancer, renal cancer, and melanoma.

Edwards teaches a method for determining the optimal α-interferon dosage for the purpose of increasing NK lymphocyte cytotoxicity. Edwards finds that a peak NK cell activation, corresponding to a mean threefold increase above preinjection levels of NK cell activity results from injection of 3 X 10^6 U injected intramuscularly. Therefore, Edwards teaches a method of establishing a baseline NK lymphocyte cytotoxicity level and then injection of an immunostimulatory dosage of α-interferon increases NK lymphocyte cytotoxicity at least about 75% above said baseline natural killer lymphocyte cytotoxicity. Edwards teaches the method in breast, ovarian, head and neck carcinoma and renal cancer patients. Edwards teaches effector to target cell ratios of 3.125:1, 6,25:1, 12.5:1, 501 and 100:1 (page 1908, 2nd column to 1909, 2nd column). Edwards fails to teach a method that includes a step of surgically resecting the tumor.

However, Nichols teaches a method where α-interferon, in combination with IL-2, is administered to a patient prior to surgery for the purpose of increasing NK cell cytotoxicity. Nichols teaches that the raionale for such a method is that immunotherapy may be used to increase immune function at the time of surgery to lessen the attenuation of host defenses, which increases the risk of tumor dissemination when tumor cells are shed into the circulation at operation.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Edwards to determine the appropriate dosage of α-interferon for the treatment of cancer patients prior to surgery for the purpose of increasing the NK cell cytoxoticity at the time of operation. One would have been motivated to have combined the teachings of Edwards with Nichols because both teach that the usefulness of α-interferon in the treatment of cancer is the ability of α-interferon to increase NK cell activity.

Conclusion

No claim is allowed. Claims 36 and 37 are objected to for depending from a rejected claim.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
November 1, 2004

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER